Complete Summary

GUIDELINE TITLE

Menopause and hormone replacement therapy (HRT): collaborative decision-making and management.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Menopause and hormone therapy (HT): collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Oct. 62 p. [138 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Menopause and perimenopause
- Osteoporosis and osteoporosis-related fractures

GUIDELINE CATEGORY

Counseling
Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To outline a process for effective collaborative decision-making regarding both treatment and prevention strategies
- To increase the percentage of perimenopausal women who receive education describing risk and benefits of hormone therapy (HT)
- To increase provider understanding of patient decisions regarding the use of hormone therapy

TARGET POPULATION

- All women interested in discussing midlife health issues
- Perimenopausal women with menopausal symptoms
- Women currently or recently using hormone therapy

INTERVENTIONS AND PRACTICES CONSIDERED

Evaluation/Management

1. Discussion of midlife health issues and menopause with patient, including healthy lifestyles, menopausal status and subtle signs of menopause, and counseling and education options
2. Discussion of menopausal symptoms and risks/benefits of therapy options, including hormone therapy (HT)
3. Assessment and discussion of disease prevention, including osteoporosis, coronary heart disease (CHD), Alzheimer's disease, colorectal cancer, skin/wound healing, tooth loss, and macular degeneration and role of HT
4. Evaluation of patient conditions for which HT might be indicated or contraindicated
5. Clarification/discussion of patient's values and priorities regarding treatment of menopausal symptoms
6. Formulation of treatment plan
7. Evaluation and management of side effects
8. Follow-up after decision to initiate HT

Treatment

1. Estrogen preparations, such as conjugated equine estrogens (Premarin®); conjugated synthetic estrogens (Cenestin®); esterified estrogens (Estratab®,

Menest®); estradiols (generic and Estrace®); estropipates (generic, Ortho-Est® and Ogen®); ethinyl estradiol (Estinyl®); estradiol transdermal systems (Esclim®, Alora®, Climara®, Estraderm®, Vivelle®, Vivelle-Dot®); vaginal estrogens (Premarin® vaginal cream, Ortho Dienestrol® vaginal cream, Estring® vaginal ring, Estrace® vaginal cream, Femring vaginal ring, and Vagifem® vaginal tablet)

2. Progesterone preparations, such as medroxyprogesterone acetate (MPA)(generic, Provera®, Cycrin®, Amen®, Curretab®); norethindrone acetate (Aygestin®); micronized oral progesterone (Prometrium®); megestrol (a synthetic progestin); norgestimate; and micronized vaginal progesterone gel (Crinone®, non-Food and Drug Administration (FDA) approved for hormone replacement therapy)
3. Estrogen-progestin combinations, such as conjugated equine estrogens + medroxyprogesterone acetate (Premphase®, Prempro®); estradiol + norethindrone (CombiPatch®, Activelle®, Femhrt®, Ortho Prefest)
4. Selective estrogen receptor modulators (SERMs), such as raloxifene (Evista®)
5. Bisphosphonates (alendronate and risedronate)
6. Calcitonin
7. Hormone and hormone-like preparations that are not approved by the FDA, such as natural progesterone cream, Tri-EST, Bi-EST, dehydroepiandrosterone (DHEA), dong quai root, and others (refer to the Annotation Appendix D in the original guideline for details).
8. Non-hormonal preparations that are approved by the FDA, but not for treatment of menopausal symptoms, such as clonidine, venlafaxine, sertraline and gabapentin
9. Non-hormonal preparations not FDA approved, such as black cohosh (remifemin), soy, evening primrose oil (EPO), chaste tree berry/vitex, ginseng

Note: This guideline does not endorse or recommend herbal remedies for menopause-related symptoms, but does include a list of non-FDA approved products, including selected herbal preparations, as a guide for clinicians.

MAJOR OUTCOMES CONSIDERED

- Patient satisfaction
- Effects of hormone therapy (HT) and other therapies on menopausal symptoms, bone mineral density, and fractures
- Risks of developing breast cancer, endometrial cancer, gallbladder disease, venous thromboembolism, or ovarian cancer with HT
- Effects of HT on cardiovascular health
- Effects of HT on Alzheimer's disease, colorectal cancer, skin/wound healing, tooth loss, and macular degeneration
- Adverse effects and complications of HT

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Clinical Validation-Pilot Testing
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Institute Partners: System-Wide Review

The guideline annotation, discussion, and measurement specification documents undergo thorough review. Written comments are solicited from clinical, measurement, and management experts from within the member groups during an eight-week review period.

Each of the Institute's participating member groups determines its own process for distributing the guideline and obtaining feedback. Clinicians are asked to suggest modifications based on their understanding of the clinical literature coupled with their clinical expertise. Representatives from all departments involved in implementation and measurement review the guideline to determine its operational impact. Measurement specifications for selected measures are developed by the Institute for Clinical Systems Improvement (ICSI) in collaboration with participating member groups following implementation of the guideline. The specifications suggest approaches to operationalizing the measure.

Guideline Work Group

Following the completion of the review period, the guideline work group meets 1 to 2 times to review the input received. The original guideline is revised as necessary, and a written response is prepared to address each of the responses received from member groups. Two members of the Guideline Oversight Group carefully review the input, the work group responses, and the revised draft of the guideline. They report to the entire committee their assessment of four questions: (1) Is there consensus among all ICSI member groups and hospitals on the content of the guideline document? (2) Has the drafting work group answered all criticisms reasonably from the member groups? (3) Within the knowledge of the appointed reviewer, is the evidence cited in the document current and not out-of-date? (4) Is the document sufficiently similar to the prior edition that a more thorough review (critical review) is not needed by the member group? The committee then either approves the guideline for release as submitted or negotiates changes with the work group representative present at the meeting.

Pilot Test

Member groups may introduce the guideline at pilot sites, providing training to the clinical staff and incorporating it into the organization's scheduling, computer, and other practice systems. Evaluation and assessment occur throughout the pilot test phase, which usually lasts for three to six months. At the end of the pilot test phase, ICSI staff and the leader of the work group conduct an interview with the member groups participating in the pilot test phase to review their experience and gather comments, suggestions, and implementation tools.

The guideline work group meets to review the pilot sites' experiences and makes the necessary revisions to the guideline, and the Guideline Oversight Group reviews the revised guideline and approves it for release.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The recommendations for menopause and hormone therapy (HT) are presented in the form of an algorithm. An algorithm is provided for Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management with 8 components, accompanied by detailed annotations. Clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III, Not Assignable) definitions are provided at the end of the "Major Recommendations" field.

Clinical Highlights for Individual Clinicians

1. There are many effective options to be considered for the relief of menopausal symptoms; although hormone therapy is often the most effective treatment, it is not always necessary. (Annotation #2A)

2. Women using hormone therapy (HT) must be regularly evaluated regarding their continued requirements for HT, especially if there has been any change in their overall health status. (Annotations #2B, 7)
3. Women who have recently discontinued HT are at risk for rapid bone loss; they must be identified and monitored appropriately to ensure continued bone health. (Annotations #2B, 2C)
4. The role of HT in disease prevention has been all but eliminated in current practice. (Annotation #2C)
5. The well-publicized results of several recent clinical trials have resulted in increased apprehension about HT among both patients and providers; discrepancies exist among various clinical studies, and it is unlikely that definitive information or consensus will be available anytime soon, if ever. (Annotations #1, 3)
6. The exact risks associated with HT, as well as possible side effects, may not be fully defined, but they cannot be dismissed and must always be considered and discussed as part of the collaborative decision-making process. (Annotations #3, 4, 6A)
7. Careful consideration and in-depth discussion are required whenever the initiation or continuation of HT is considered; help each woman clarify her individual values and priorities so that she may decide how important each of the potential benefits and risks of HT is to her unique situation. (Annotation #4)
8. Provide support and encouragement, through accessibility and close follow-up, for women who have recently initiated HT. (Annotations #6A, 7, 8)

Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management Algorithm Annotations

1. Discuss Midlife Health Issues and Menopause

   Consider initiating a discussion about these issues as part of routine health maintenance visits with women 40 years of age or older. Many women wish to begin this discussion well before menopause.

   For women on HT, regularly review and discuss its use. (See also Annotation #2b, "Discuss Options for Long-Term HT Users; Ensure Continued Bone Health".)

   There are three distinct areas for discussion and decision-making related to midlife health issues; these are reflected in the organization of this guideline:

   - Options for menopausal symptom relief
   - Options for women who have been long-term HT users and who seek advice about continuing, stopping, or modifying their regimen
   - Options for risk factor modification and disease prevention

   Encourage healthy lifestyles

   Always emphasize healthy lifestyles and lifestyle modifications as the most important first step in both menopausal symptom relief and disease prevention.

Clarify menopausal status; be alert to subtle signs of menopause

Perimenopause: irregular or no menses, often accompanied by hot flashes, night sweats, or urogenital symptoms

Menopause: complete cessation of menses for one year

In addition to inquiring about common menopausal symptoms, also ask about irritability, anxiety, sleeplessness, and agitation; some women may not consider these symptoms to be menopausal or may be embarrassed to volunteer information about them.

Laboratory testing is usually not necessary to establish menopausal status

Clarifying whether or not a woman is perimenopausal or menopausal is usually a clinical diagnosis and laboratory testing is not required.

For women with apparent menopausal symptoms who are younger than average, or who continue to have apparently regular menses, testing may be useful; measure both follicle stimulating hormone (FSH) and estradiol (E2).

Testing may be most useful for the woman on oral contraceptives (OCPs) who is interested in determining whether or not she is menopausal and can stop medication; measure FSH and estradiol as late as possible in the placebo week of pills.

Discuss current role of hormone therapy; address patient concerns

Hormone therapy is the most effective treatment for hot flashes, urogenital symptoms, and other menopausal symptoms. However, it is not always necessary, and other options frequently provide adequate relief.

As a result of several recent studies, most notably the Women's Health Initiative (WHI), and over a relatively short period of time, the use of long-term HT for the prevention of various chronic diseases has all but ceased. Although HT did protect against osteoporosis-related fractures and colorectal cancer in the WHI, cardiac protection could not be demonstrated. There was, as expected, an increased risk of breast cancer, stroke, and venous thrombosis in the combination HT (Prempro) arm; this portion of the WHI was halted because the observed benefits were not as great as originally hoped and did not outweigh the observed risks.

Discrepancies among the various studies continue to be debated, and it is unlikely that definitive information or consensus will be available anytime soon, if ever. Acknowledge this uncertainty and take the necessary time for an in-depth discussion with women who are considering either starting or continuing hormone therapy. It is often helpful to discuss the patient's understanding and perception of the risks of HT and of various conditions and to help put them in perspective.

Ask about alternative therapies

A variety of herbal preparations and dietary supplements are marketed and used by patients as natural alternatives to hormone therapy. However, unless specifically asked, patients often do not volunteer information about their use.

These products may contain biologically active ingredients with significant physiologic effects. Their exact composition and consistency may be unknown or inconsistent. Very few products have been evaluated by well-controlled studies.

Patients will be well served and providers will gain credibility if factual information about alternative therapies is made available in a non-judgmental way. A strategy for guiding a discussion about the use, the known risks, and the potential benefits of several alternative therapies commonly used by menopausal women is included in Annotation Appendix D, "Non-FDA-Approved Products."

Counseling and education strategies

Women who actively participate in individualized, collaborative decision making which reflects their values and priorities are more satisfied with their ultimate choices and are more committed to their treatment.

Consider presenting information in a variety of formats, including Internet sites and discussion groups.

2. a. Discuss Options for Menopausal Symptom Relief

Prior to menopause, often for several years, rising serum FSH levels and erratic ovarian follicle maturation lead to fluctuating and unpredictable estrogen and progesterone levels, accounting for many menopausal symptoms.

Most commonly, perimenopausal women experience menstrual irregularities, hot flashes, and vaginal dryness of varying degrees and severity. The sleep disruption from hot flashes may also lead to irritability, forgetfulness, and inability to concentrate. Fluctuating hormone levels are associated with emotional lability, but are not felt to be a direct cause of depression. Both disrupted sleep as well as urogenital changes can affect sexual functioning.

For many women, these symptoms are mild and of short duration and do not require treatment beyond lifestyle adjustments, education, and reassurance.

For others, these symptoms may cause significant morbidity and require additional treatment. Estrogen therapy is most effective, although various non-hormonal alternatives are sometimes helpful.

Hot Flashes and Night Sweats

Most women experience hot flashes (flushes) to some degree during the perimenopause, although fewer than half consider them to be a significant problem.

Characteristically, the hot flash involves an intermittent sensation of heat, flushing, and perspiration, usually limited to the head and upper torso. Some women report a prodrome of head pressure. The flushing is sometimes reported to be associated with palpitations and episodes of feeling faint. Hot flashes occurring during the night are commonly called night sweats.

Serum levels of FSH do not correlate with either intensity or frequency of hot flashes; it is the fluctuation in estrogen levels that seems to be of greater significance. Hot flashes usually subside within five years of the menopause.

In younger women, oophorectomy results in a precipitous decline in estrogen levels, causing generally more severe hot flashes than those experienced by women entering menopause spontaneously.

Lifestyle modifications such as exercise, lighter clothing, sleeping in a cooler room, and reducing stress may be sufficient to manage hot flashes for many women. Avoidance of possible triggers, including spicy foods, caffeine, smoking, and alcohol may help.

Hormone therapy is the most effective means of relieving hot flashes. Therapy is usually limited to, at most, a few years, and although the absolute risks are very low, they still must be fully discussed.

Following oophorectomy, women are much more likely to require hormone therapy, often in higher doses, to relieve what are often more severe hot flashes.

Selective estrogen receptor modulators (SERMs) are not indicated for menopausal symptom relief; they may actually worsen hot flashes.

Progestogens such as megestrol have been shown to reduce flushing, although to a markedly lesser extent.

Non-hormonal therapies with proven efficacy for hot flashes include clonidine, gabapentin, and the antidepressants fluoxetine, paroxetine, and venlafaxine. While often effective, these agents are of lesser efficacy than HT.

Bellergal and alpha-methyldopa have often been used, but no well-done studies support their efficacy.

Phytoestrogens and isoflavones, soy products/isoflavones, either through diet or supplementation, may not reduce the incidence of hot flashes. Inconsistencies among studies to date may be explained by different doses, products, sources, and processing. [Conclusion Grade III: See Discussion Appendix A, Conclusion Grading Worksheet — Annotation #2a (Soy Products) in the original guideline document]

Herbal preparations and dietary supplements are commonly used but poorly studied; these include black cohosh, dong quai, evening primrose oil, flaxseed, ginseng, mai quan, progesterone creams, red clover, and wild yam extract. See Appendix D, "Non-FDA-Approved Products" on the original guideline for more information about these agents.

Mood and Anxiety Disturbances

There is a complex interplay between fluctuating hormone levels and mood. The connection between mood lability and anxiety on the one hand, and other menopausal symptoms, especially disturbed sleep, on the other, is also complicated. Social changes affecting menopausal women can also affect their mood and sense of well-being.

Women with a history of depression have a higher risk of menopausal mood disorders, but there is no direct association between menopause and depression. There is some evidence that estrogen may potentiate the effects of antidepressants, possibly by increasing or maintaining serotonin levels. Progestins may aggravate mood disturbances, perhaps negating any benefits of estrogen.

Lifestyle changes, including adequate sleep, regular physical activity, and relaxation exercises may help with anxiety symptoms.

Hormone therapy is most likely to be helpful if there are other menopausal symptoms present. It is not known if estrogen has a direct effect on mood, irritability, or anxiety, or whether these effects are due solely to the alleviation of hot flashes and sleep disturbances.

Non-hormonal therapies (selective serotonin reuptake inhibitors [SSRIs]) are most helpful if the underlying problem is a primary mood disorder or depression rather than a manifestation of hot flashes or disturbed sleep.

Concentration Difficulties and Forgetfulness

Menopausal women often report difficulties with concentration and short-term memory. The direct association of these symptoms with female hormone levels, while biologically plausible, is unproven.

There is little, if any, evidence of any relationship between these mild, subjective symptoms and the later development of dementia; these are separate clinical entities and it is important to make this distinction clear when counseling patients. (Current concepts regarding dementia and HT are discussed in Annotation and Discussion 2c, "Discuss Options for Limited Role of HT for Disease Prevention." in the original guideline.)

Lifestyle factors, especially exercise and sleep hygiene, appear to be just as helpful for improving subjective cognitive symptoms as other alternatives.

Hormone therapy may improve cognitive complaints that are related to disturbed sleep or other menopausal symptoms. If HT has any direct effect, it is relatively minor.

Sleep Disturbances

Not all sleep disorders among menopausal women are related to hormonal changes; mood disorders or primary sleep disorders must also be considered.

Among menopausal-related sleep disturbances, night sweats are frequently the underlying cause, but some women may experience sleep disturbances without hot flashes.

Older women who discontinue HT after many years of use may develop new-onset sleep disturbances. These may be their only complaints and may not be recognized as being related to HT cessation.

Lifestyle management includes avoiding exercise late in the day, regular bedtimes, or a hot shower or bath immediately prior to going to bed. Over-the-counter sleep aids may also be helpful.

Hormonal therapy estrogen will often relieve and improve sleep by the alleviation of night sweats. In addition, women frequently report an improvement in sleep patterns with HT even if hot flashes or night sweats are not prominent features of their menopausal symptoms.

Decreased Libido and Sexual Dysfunction

Night sweats, mood lability, vaginal dryness, and sleep disturbances may significantly affect sexual function. In addition, menopausal women confront significant social changes regarding their own sense of well-being and the sexuality of their partners; an exploration of these social issues is time well spent.

Hormone therapy: Besides relieving hot flashes and improving sleep, HT improves urogenital atrophy, thinning, dryness, and loss of elasticity, all which may cause dyspareunia. While this will improve sexual functioning for many women, HT has no proven direct effect on sexuality or libido.

Non-hormonal therapies: Selective serotonin reuptake inhibitors (SSRIs) may help sexual dysfunction due to depression or other mood disorders. In some situations, anorgasmia may respond to sildenafil.

Androgen supplementation, particularly after surgical menopause, has been proven to increase libido. Standard doses have not been established and a wide range of doses, with potentially serious side effects, is often quoted in the literature. All women must have careful counseling before starting these agents. The partial androgenic properties of tibolone may have a beneficial effect on libido for some women.

Vaginal Dryness, Incontinence and Urgency

Urogenital tissues are highly estrogen-sensitive; vaginal dryness, vulvovaginal irritation, urinary urgency and irritation, more frequent urinary tract infections, urinary incontinence, and pelvic support problems are increasingly common following menopause. Atrophy and lack of lubrication may cause dyspareunia.

The relationship between urinary incontinence and menopause is not well understood. Estrogen was long thought helpful in the treatment of incontinence, but newer evidence suggests that it may actually exacerbate the problem. Most studies have shown little improvement in urinary stress incontinence, although urge incontinence may be more responsive to HT.

Hormone therapy: While nonprescription vaginal lubricants and moisturizers may provide some relief, estrogens are far superior. Topical estrogens are preferred; there is little systemic absorption with commonly used dosages and minimal risk of side effects or endometrial hyperplasia. Vaginal estrogens significantly reduce the rate of recurrent urinary tract infections compared to placebo.

See Annotation #6 for specific guidelines for various vaginal estrogen preparations and delivery systems.

Headache

Among their many causes, headaches may be associated with fluctuating estrogen levels in perimenopause.

Hormone therapy may stabilize hormone levels and alleviate headache symptoms. There are no contraindications to HT in women with migraines.

HT may occasionally cause or aggravate headaches; see Annotation #7, "Evaluate and Manage Side Effects" for guidelines for adjusting HT in these situations.

Other causes of headache and their treatment are discussed in the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) guideline Migraine Headache.

2. b. Discuss Options for Long-Term HT Users; Ensure Continued Bone Health

Women who have recently discontinued HT are at risk for rapid bone loss; they must be identified and monitored appropriately to ensure continued bone health.

Until recently, women who had been on HT without any problems rarely considered changing their regimens. With the termination of one arm of the WHI trial and in the face of continued concern about HT, many women have discontinued it on their own; some have done well and others have experienced a recurrence of hot flashes and other symptoms. In addition,

some women may be reluctant to volunteer this information unless specifically asked.

Some women want advice about strategies for stopping HT while minimizing symptoms, others wish reassurance about continuing HT, and still others want information about different formulations or regimens that may be safer in some way.

The actual risks of continuing HT are very low, but they cannot be dismissed and need to be addressed.

While many different formulations and regimens for hormone therapy have been suggested and are being used by many practitioners, there is very little firm data to support these recommendations or guide this process.

No matter how long a woman has been on HT, she may undergo rapid bone loss upon stopping; carefully monitor bone density and counsel her about continued bone health. See the NGC summary of the ICSI guideline, Diagnosis and Treatment of Osteoporosis for specific management information.

Regularly evaluate each woman's need for hormone therapy.

- Consider the original indication for HT and whether it still remains.
- Check for the development of any medical conditions, particularly coronary heart disease (CHD), which might mandate greater caution.
- If HT is still indicated, consider whether a lower dose or different formulation might be more appropriate.

There is no evidence that different formulations or dosing regimens are any safer than those which have been better studied or more widely used (conjugated equine estrogens and medroxyprogesterone acetate [CEE/MPA]).

See Annotations 6b, "Guidelines for Modifying Hormone Therapy in Long-Term Users" and 6c, "Guidelines for Discontinuing Hormone Therapy in Long-Term Users" for guidelines for modifying hormone therapy regimens.

2. c. Discuss Options for Limited Role of HT for Disease Prevention

While HT has recently been proven to prevent osteoporotic fractures and lower the risk of colon cancer, current practice largely limits its role to the treatment of menopausal symptoms.

HT is rarely, if ever, initiated solely for long-term disease prevention. However, given the changing perceptions and uncertainty about the role of HT, current concepts regarding its relationship to several chronic conditions are summarized below.

Osteoporosis: Prevention of osteoporosis has been the most well-documented and widely accepted use of HT. While observational studies had indicated that HT provided significant protection against hip, vertebral, and

wrist fractures, the Women's Health Initiative (WHI) was the first randomized trial to confirm this finding.

The benefits of HT are maintained as long as it is continued, but bone loss resumes when treatment is stopped, and any residual benefit is rapidly lost.

HT is as effective as other agents in preventing fracture due to osteoporosis; these include:

Bisphosphonates — alendronate (Fosamax), risedronate (Actonel) — are commonly used for both prevention and treatment of osteoporosis. Their use may be complicated by esophageal irritation, but weekly or monthly dosing or even yearly intravenous infusion minimizes this problem.

Bisphosphonates in combination with estrogen are more effective than either agent alone.

Selective estrogen receptor modulators (SERMs) — raloxifene (Evista) — are indicated for the prevention and treatment of osteoporosis. They are not indicated for the treatment of menopausal symptoms and may even aggravate hot flashes in some women.

Calcitonin nasal spray, used for osteoporosis treatment, inhibits bone resorption and reduces fracture rates. Nasal irritation and cost limit its use.

Refer to the NGC summary of the ICSI guideline Diagnosis and Treatment of Osteoporosis for specific recommendations for prevention and treatment.

Coronary heart disease (CHD): Recent data has called into question the long-held belief that HT protects against the development and progression of CHD. Many observational studies and known biologic effects suggested a beneficial effect of estrogen for CHD prevention. However, more recent prospective randomized controlled trials (WHI, others) have not shown any benefit of HT for either primary or secondary prevention, and have even suggested that HT may cause myocardial infarction.

These discrepancies continue to be hotly debated. The observational studies may have been affected by selection bias, in that healthier women with better access to health care are more likely to use HT. Alternatively, the prospective trials may have been confounded by the inclusion of older women with pre-existing CHD; while estrogen given in early menopause may prevent atherosclerosis, later estrogen use, after lesions develop, may actually precipitate coronary events.

Progestins may also account for the deleterious effects of HT; however, there is no specific evidence that estrogen alone is safer or more beneficial.

Specific recommendations:

- Identify and treat all CHD risk factors.
- Do not initiate HT for the prevention of CHD.
- Do not initiate HT in patients with known CHD.
- If CHD develops while on HT, consider other alternatives.

Alzheimer's disease (AD): Some studies have indicated that HT may improve cognitive functioning in perimenopausal women, but this may be due solely to the alleviation of menopausal symptoms. It is unknown whether long-term HT has any benefit for the prevention or progression of dementia, including AD. More recent studies have reported an increased risk of dementia among older women taking HT.

Again, these discrepancies may be explained by selection bias, by the inclusion of older women who were past a "window" in early menopause when HT would have been helpful, or by other factors. As with the controversy surrounding CHD, the exact relationship between AD and HT is uncertain and may remain so for quite some time.

Colorectal cancer: The WHI confirmed that HT lowers the risk of developing colon cancer. However, HT should not be used solely for colon cancer prevention.

Women taking HT still need colorectal cancer screening at the recommended intervals.

Skin/Wound healing: HT has beneficial effects on collagen metabolism, improving skin tone and wound healing.

Tooth loss: HT reduces maxillary and mandibular osteoporosis and prevents resulting tooth loss.

Macular degeneration: HT reduces the risk of developing macular degeneration.

3. Discuss HT Risks and Contraindications

Breast cancer: The possible increased risk of breast cancer with HT is a primary concern of many women. Even though many authorities view this increase as statistically insignificant or even spurious, it cannot be ignored and the limitations of current knowledge must be discussed.

There are currently opposing views on the effects of hormone therapy on the risk of breast cancer. Recent studies raise the question that estrogen and progestin may increase the relative risk of breast cancer beyond that associated with estrogen alone.

There may be a small increase in breast cancer risk after 5 to 15 years or more of hormone therapy. This increased risk seems to be only in current and not prior users of HT. Women who take HT for less than 5 years (e.g., for menopausal symptoms) may not be at increased risk.

Breast cancer mortality does not seem to be increased with hormone therapy. Breast cancers that arise while a woman is on HT may tend to be less advanced and to have a more favorable prognosis; on the other hand, this effect may be due simply to earlier detection.

Endometrial cancer: The risk of developing endometrial cancer is increased only in women taking unopposed estrogen. Any additional risk is largely eliminated when progestin is added to the HT regimen. Women who have had a hysterectomy can take unopposed estrogen without increased risk.

Women with an intact uterus who are unable to tolerate progestin and are taking unopposed estrogen must have annual endometrial monitoring by means of either biopsy or transvaginal ultrasound. (See Annotation #7, "Evaluate and Manage Side Effects.")

Gallbladder disease: The risk of gallbladder disease continues at higher, premenopausal levels in women taking HT.

Venous thromboembolism (VTE): The risk for VTE appears to be increased approximately twofold in current, but not former users of HT. The absolute risk is still relatively low, being increased from approximately 15 cases per 100,000 women in the general population to approximately 30 cases per 100,000 women on HT.

Myocardial infarction: There does not appear to be an overall effect on the rate of nonfatal myocardial infarction associated with an HT regimen.

Alzheimer's disease: There are discrepancies in the evidence that estrogen has any specific effects on cognitive performance.

Ovarian cancer: There may be a weak association between the prolonged use of estrogen and ovarian cancer, but no epidemiological evidence has been established.

Unexplained vaginal bleeding and pregnancy are temporary but absolute contraindications to HT.

Past history of breast cancer, endometrial cancer, or venous thrombosis are usually considered absolute contraindications to HT; the rare exception is beyond the scope of this guideline.

Family history of premenopausal breast cancer: It is not known if HT causes any greater increase in breast cancer risk in women with a family history than in average-risk women.

Hypertriglyceridemia is a contraindication to oral conjugated estrogens because of the danger of precipitating pancreatitis. It is safe to use transdermal estrogen, esterified estrogens, and estradiol in these patients. (See Discussion #3, "Discuss HT Risks and Contraindications" for details.)

Chronic liver disease is a relative contraindication to HT. Transdermal and intra-vaginal estrogen avoids the first-pass hepatic effect of oral HT.

HT is not contraindicated in the presence of certain clinical conditions where many practitioners are reluctant (often unjustifiably so) to recommend oral contraceptives; OCPs have much more potent estrogenic effects than HT. These conditions include:

- endometriosis
- fibrocystic breast disease
- hypertension
- mastalgia
- migraine headaches
- obesity
- tobacco use
- uterine leiomyomata (fibroids)

4. Collaborative Decision-Making: Clarify Patient's Values and Priorities

Truly collaborative decision-making requires that each woman clarify her individual values and priorities, with help from her provider if she wishes, so that she may decide how important each of the potential benefits and risks of HT is to her unique situation.

Inquire about each woman's particular goals and concerns about menopause and her attitudes toward taking medications in general and hormone therapy in particular.

Acknowledge that discrepancies among the various studies continue to be debated, and it is unlikely that definitive information or consensus will be available anytime soon, if ever. It is often helpful to discuss the patient's understanding and perception of the risks of hormone therapy and of various conditions and to help put them in perspective. Clarifying the distinction between relative and absolute risk is also sometimes helpful.

Individual women, even if they have identical clinical situations, will often arrive at completely different decisions regarding hormone therapy. As long as the decision is right for each individual patient, it is the appropriate choice.

6. a. Guidelines for Initiating Hormone Therapy

Jointly decide on the hormone therapy regimen best suited to each woman's particular characteristics and needs.

There is no firm evidence that any one form of estrogen or progestin is superior to another, although different preparations are useful in different clinical settings.

<u>Estrogen-Progestin (Combined) vs. Estrogen-Only Hormone Therapy</u>

Progestogens are combined with estrogen to prevent endometrial hyperplasia and to minimize the risk of endometrial cancer in women with an intact uterus.

Progestogens are not necessary in women who have had a hysterectomy.

Please refer to Table 1 "Combination Estrogen-Progestin Preparations" in the original guideline document for information on delivery mode and dosage.

Cyclic vs. Continuous Combined Hormone Therapy

The terms cyclic and continuous refer only to the progestogen component of combined HT.

Estrogen should always be given every day; there is no advantage to the once popular intermittent dosing as it may cause increased hot flashes or migraines during the time that estrogen is withheld.

Progesterone may be given either cyclically (generally in the earlier years of perimenopause) or continuously (generally later in menopause) as detailed below.

Discuss Expected Bleeding Patterns

Younger women with occasional menses may still be having intermittent ovarian activity. Initiating HT with a cyclic progestin regimen minimizes irregular bleeding and spotting and usually results in a predictable monthly withdrawal bleed. Some women may achieve eventual amenorrhea, although it may require several months or longer.

Older women who have been on cyclic therapy for two to three years may be switched to continuous combined HT. If they have been amenorrheic on cyclic HT, they are likely to remain so on combination HT. However, even if they have been having light withdrawal bleeding, they may still become amenorrheic on combined HT.

Theoretically, menopausal women who have been amenorrheic for some time could be started directly on combination therapy, but as a practical matter, HT is rarely initiated in these women.

Continuous progestin may cause unpredictable vaginal bleeding, with or without spotting, for many months. Five to 20% of these women may never achieve amenorrhea and may opt for cyclic hormone therapy to achieve a more predictable bleeding pattern.

Discuss Possible Side Effects

Estrogenic side effects may include mastalgia (breast tenderness), fluid retention, nausea, leg cramps, and aggravation of headaches. Rarely, estrogen may cause an unexpected rise in blood pressure.

Reassure women with mastalgia that it is not in any way associated with an increased risk of breast cancer.

Progestin side effects may include fluid retention and bloating, headache, mastalgia (breast tenderness), oily skin and acne, mood alterations, and premenstrual type symptoms.

Refer to Annotation #7, "Evaluate and Manage Side Effects," for further details and specific management guidelines.

Estrogen preparations

Please refer to Table 2, "Estrogen Preparations" at the end of Annotation 6a in the original guideline for information on delivery mode and dosage of estrogen preparations.

Progesterone/Progestin preparations

Please refer to Table 3, "Progestin Preparations" at the end of Annotation 6a in the original guideline for information on delivery mode and dosage of estrogen preparations.

Estrogen-Androgen preparations

Add androgen to the regimen for libido and mood disturbances only if standard HT has not been successful.

Dosage: methyltestosterone 2.5 mg and esterified estrogens 1.25 mg (Estratest); methyltestosterone 1.25 mg and esterified estrogens 0.625 mg (Estratest HS)

Please refer to Table 2, "Estrogen Preparations" in the original guideline for information on delivery mode and dosage.

Hormone Therapy for Hot Flashes

CEE 0.3 mg daily may be effective.

Following surgical menopause, some women may require as much as CEE 2.5 mg daily.

Estradiol 0.5 to 1.0 mg daily may be effective.

Hormone Therapy for Urogenital Symptoms

If needed only for urogenital symptoms, consider intravaginal estrogens.

Systemic estrogens (oral or transdermal) may be required to have an effect on urinary epithelium for alleviation of frequency, urgency, incontinence.

Estrogen cream: CEE 1 to 2 weekly after initial treatment (see above)

Estrogen ring (Estring)

Women who may still need contraception

For perimenopausal women over age 35 who may still need contraception, OCPs are a safe alternative to HT provided these women do not smoke and are otherwise healthy. Prescribe low-estrogen OCPs to minimize any risk of thromboembolic events.

Younger perimenopausal women with irregular menses and hot flashes may still be occasionally ovulating. Consider low-dose OCPs rather than HT to control symptoms, and minimize irregular bleeding while providing still-needed contraception.

6. b. Guidelines for Modifying Hormone Therapy in Long-Term Users

While many different formulations and regimens have been suggested and are being used by many practitioners, there is very little firm data to support these recommendations or guide this process.

There is no evidence that different formulations or dosing regimens are any safer than those which have been better studied or more widely used (conjugated equine estrogens [CEE]/medroxyprogesterone acetate [MPA]). However, many older women may be able to decrease their dose of estrogen without precipitating the resumption of hot flashes.

Women may undergo rapid bone loss immediately after stopping HT. Carefully monitor bone density within the first year. While there is good evidence that lower doses of estrogen (CEE 0.3 mg daily, estradiol 0.5 mg daily, or equivalent) maintain bone density as well as higher, better studied doses, it is not known if protection against fractures is similarly maintained.

While transdermal estrogen has a better side effect profile than oral estrogens and biological plausibility for a lower-risk profile, there is no evidence that transdermal estrogen has a lower risk of VTE, stroke, or cardiac events.

It has been postulated that the progestogen in combination HT is responsible for increasing breast cancer risk as well decreasing the benefits of HT. Accordingly, some practitioners limit the progestogen component, and consequently withdrawal bleeding, to once every 3 to 4 months. While this is an increasingly common practice, there is no evidence that this provides adequate protection against endometrial hyperplasia.

There is certainly no evidence to support the use of unopposed estrogen, no matter how frequently or aggressively endometrial surveillance is done.

6. c. Guidelines for Discontinuing Hormone Therapy in Long-Term Users

Many different regimens have been suggested and are being used by many practitioners for discontinuing hormone therapy in long-term users, but there is very little firm data to support these recommendations or guide this process.

Many women do not notice any symptoms even with abrupt cessation of HT, while others may experience a recurrence of hot flashes. In older menopausal women, sleep disorders, rather than hot flashes, may be the major manifestation of renewed menopausal symptoms.

There is some biologic basis for recommending tapering hormone therapy over several months rather than stopping abruptly. As the washout period of CEE is longer than with other forms of estrogen, switching to a different formulation, such as estradiol, may also be helpful.

Consider alternative therapies for menopausal symptom relief, as outlined in Section 2a, while tapering HT.

As noted before, no matter how long a woman has been on HT, she may undergo rapid bone loss upon stopping; bone health, specifically bone density, must be considered and carefully monitored.

7. Evaluate and Manage Side Effects

The decision to take HT is often reached after considerable soul-searching by the patient. Her continued use of HT will likely be further dependent on the nature and resolution of any significant side effects that result from taking HT. The provider needs to be mindful that compliance with HT, problematic at best, will likely be worse if side effect concerns are not dealt with in a quick, thorough manner.

The list of potential side effects from HT is extensive, and the remainder of this annotation is not meant to be exhaustive. What are addressed here are the side effects most often associated with compliance concerns.

Vaginal Bleeding

See "Discuss expected bleeding patterns" in Annotation #6a, "Guidelines for Initiating Hormone Therapy" for a summary of expected patterns of continued or irregular vaginal bleeding.

For most women, irregular vaginal bleeding improves within approximately six months of initiating HT; try to avoid changing HT regimens or formulations too quickly.

Evaluation and management of "abnormal" vaginal bleeding?

There are no universally accepted criteria for defining "abnormal" bleeding and mandating further evaluation. We believe the following criteria are reasonably cautious but minimize unnecessary endometrial biopsies.

Women on cyclic HT: Normal bleeding should occur near the end of the progestogen phase of the cycle. Evaluate any significant change in the normal pattern or any breakthrough bleeding occurring at other times.

Women on continuous HT: Evaluate any bleeding which commences after six months of amenorrhea or which persists after six months of HT.

Refer to the Discussion Section in the original guideline document for more detailed information regarding the various modalities used to evaluate abnormal bleeding, including endometrial sampling (biopsy or dilation and curettage [D & C]), endovaginal ultrasound (EVUS), sonohysterography, and hysteroscopy.

Management of bleeding occurring while on cyclic hormone therapy

Variations in bleeding patterns among younger women taking cyclic HRT are common; these usually resolve spontaneously when ovarian function ceases completely.

Women who have been amenorrheic for many years may experience a resumption of bleeding after initiating cyclic HT; switching to continuous HT may help.

If endometrial biopsy shows persistent proliferative activity during the progestogen phase, increase the progestogen dose if tolerated.

Management of bleeding occurring while on continuous hormone therapy

Irregular spotting and bleeding may persist for many months after switching from cyclic to continuous HT, even in women who have been amenorrheic for some time.

This bleeding is usually due to an unstable atrophic endometrium and may also resolve with an increased progestogen dose. Another option is a levonorgestrel-secreting intrauterine device (IUD) instead of oral progestogens. An increased estrogen dose may also be tried, provided the evaluation was normal.

Many women will end up switching back to cyclic HT so that their bleeding pattern is at least predictable. They do not necessarily have to cycle monthly; a withdrawal bleed every 3 to 4 months is sufficient to prevent endometrial hyperplasia.

Weight Gain

Around menopause, most women gain weight and experience an increase in their proportion of central abdominal fat. Contrary to various widely-held beliefs, this is neither caused nor alleviated by hormone therapy.

Some women experience breast tenderness and fluid retention shortly after initiating HT and these symptoms may contribute to a subjective sense of weight gain; they will usually resolve after a few months.

Patient education that anticipates concerns about weight gain may be helpful. Weighing patients at each visit may help reassure them that although their body fat distribution may change, their actual weights over time are relatively stable.

Headache

As discussed in more detail in Annotation 2a, estrogen therapy may occasionally aggravate migraine headaches. Switching to a lower dose or from oral to transdermal estrogen (with more even absorption) may be helpful.

Estrogenic Side Effects

Common estrogenic side effects are listed in Annotation #6a, "Guidelines for Initiating Hormone Therapy."

Fluid retention and headache may be related to either estrogen or progestogens; modifying the progestogen first is usually the better strategy (see below).

Breast tenderness (mastalgia) is more likely to be alleviated with lower estrogen dosages, although adjusting the progestogen may occasionally be effective if the symptoms seem to have a cyclic quality (see below).

Switching to the transdermal estrogen preparations may alleviate nausea.

Progestogenic Side Effects

Common progestogenic side effects are listed in Annotation 6a, "Guidelines for Initiating Hormone Therapy."

Fluid retention and headache are most likely related to progestogens. However, if a different formulation of progestogen is not helpful, consider modifying the estrogen component (see above).

Although MPA has been among the most widely used progestogens, other agents, especially micronized progesterone (Prometrium) may be better tolerated.

Continuous HT, with more constant systemic absorption than cyclic HT, may be tried for the relief of mastalgia, headaches, and premenstrual-type symptoms if adjusting the two components individually is not effective.

The levonorgestrel-secreting IUD and vaginal progesterone suppositories keep systemic absorption to an absolute minimum while still providing adequate endometrial protection.

Using cyclic progestogens for a full 14 days but only every 3 months also minimizes the frequency of side effects, but it is not known whether this regimen provides as much endometrial protection as standard monthly HT.

8. Follow-Up/See Related ICSI Guidelines

Follow-up within a few weeks after initiating hormone therapy. Many women who discontinue HT do so without further discussion with their healthcare providers.

Regularly evaluate each woman's need for hormone therapy.

- Consider the original indication for HT and whether it still remains.
- Check for the development of any medical conditions, particularly CHD, which might mandate greater caution.
- If HT is still indicated, consider whether a lower dose or different formulation might be more appropriate.

Women may undergo rapid bone loss upon stopping hormone therapy. For women who may have stopped HT since their last encounter, consider bone density measurement.

The standards of practice for menopause management and hormone therapy are rapidly changing.

Be aware of any new clinical studies or practice guidelines that become available.

Definitions:

Conclusion Grades:

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to

the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided for Menopause and Hormone Therapy (HT): Collaborative Decision-Making and Management.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The guideline contains an annotated bibliography and discussion of the evidence supporting the recommendations. The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Benefits of Hormone Therapy (HT) for Relief of Symptoms

- Hot flashes – HT is the most effective means of relieving hot flashes. Therapy is usually limited to, at most, a few years, and although the absolute risks are very low, they still must be fully discussed.
- Mood and Anxiety Disturbances – HT is most likely to be helpful if there are other menopausal symptoms present. It is not known if estrogen has a direct effect on mood, irritability, or anxiety, or whether these effects are due solely to the alleviation of hot flashes and sleep disturbances.
- Concentration Difficulties and Forgetfulness - HT may improve cognitive complaints that are related to disturbed sleep or other menopausal symptoms.
- Sleep Disturbances - Estrogen will often relieve and improve sleep by the alleviation of night sweats. In addition, women frequently report an improvement in sleep patterns with HT even if hot flashes or night sweats are not prominent features of their menopausal symptoms.
- Decreased Libido and Sexual Dysfunction - Besides relieving hot flashes and improving sleep, HT improves urogenital atrophy, thinning, dryness, and loss of elasticity, all which may cause dyspareunia. While this will improve sexual functioning for many women, HT has no proven direct effect on sexuality or libido.
- Vaginal Dryness, Incontinence and Urgency - While nonprescription vaginal lubricants and moisturizers may provide some relief, estrogens are far superior. Topical estrogens are preferred; there is little systemic absorption with commonly used dosages and minimal risk of side effects or endometrial hyperplasia. Vaginal estrogens significantly reduce the rate of recurrent urinary tract infections compared to placebo.

- Headache – HT may stabilize hormone levels and alleviate headache symptoms.

Benefits of HT for Preventive Therapy

- Osteoporosis - Prevention of osteoporosis has been the most well-documented and widely accepted use of HT. While observational studies had indicated that HT provided significant protection against hip, vertebral, and wrist fractures, the Women's Health Initiative (WHI) was the first randomized trial to confirm this finding.

  The benefits of HT are maintained as long as it is continued, but bone loss resumes when treatment is stopped, and any residual benefit is rapidly lost.

- Coronary heart disease (CHD) – Recent data have called into question the long-held belief that hormone replacement therapy protects against the development and progression of coronary heart disease.
- Alzheimer's Disease – HT may improve cognitive functioning in perimenopausal women, but this may be due solely to the alleviation of menopausal symptoms. It is unknown whether long-term HT has any benefit for the prevention or progression of dementia, including Alzheimer's disease.
- Colorectal Cancer – The Women's Health Initiative confirmed that HT lowers the risk of developing colon cancer. However, HT should not be used solely for colon cancer prevention.
- Skin/Wound Healing – HT has beneficial effects on collagen metabolism, improving skin tone and wound healing.
- Tooth Loss – HT reduces maxillary and mandibular osteoporosis and prevents the resulting tooth loss.
- Macular Degeneration – HT reduces the risk of developing macular degeneration.

POTENTIAL HARMS

Risks of Hormone Therapy (HT)

- Breast Cancer - The possible increased risk of breast cancer with hormone therapy (HT) is a primary concern of many women.

  There are currently opposing views on the effects of hormone therapy on the risk of breast cancer. Recent studies raise the question that estrogen and progestin may increase the relative risk of breast cancer beyond that associated with estrogen alone.

  There may be a small increase in breast cancer risk after 5 to 15 years or more of hormone therapy. This increased risk seems to be only in current and not prior users of HT. Women who take HT for less than 5 years (e.g., for menopausal symptoms) may not be at increased risk.

  Breast cancer mortality does not seem to be increased with hormone therapy. Breast cancers that arise while a woman is on HT may tend to be less

advanced and to have a more favorable prognosis; on the other hand, this effect may be due simply to earlier detection.

- Endometrial Cancer - The risk of developing endometrial cancer is increased only in women taking unopposed estrogen. Any additional risk is largely eliminated when progestin is added to the HT regimen. Women who have had a hysterectomy can take unopposed estrogen without any increased risk. Women with an intact uterus who are unable to tolerate progestin and are taking unopposed estrogen must have annual endometrial monitoring by means of either biopsy or endovaginal ultrasound.
- Gallbladder Disease - The risk of gallbladder disease continues at higher, premenopausal levels in women taking HT.
- Venous Thromboembolism (VTE) - The risk for venous thromboembolism appears to be increased approximately twofold in current, but not former, users of HT. The absolute risk is still relatively low, being increased from approximately 15 cases per 100,000 women in the general population, to approximately 30 cases per 100,000 women on HT.
- Ovarian Cancer - There may be a weak association between the prolonged use of estrogen and ovarian cancer, but no epidemiological evidence has been established.

Side Effects

- Bleeding or spotting is the most frequent side effect of hormone therapy and the main reason that women discontinue its use.
- Estrogenic side effects include mastalgia, fluid retention, nausea, leg cramps, and aggravation of headaches. Rarely, estrogen may cause an unexpected rise in blood pressure.
- Progestin side effects may include fluid retention and bloating, headache, mastalgia, oily skin and acne, mood alterations, and premenstrual-type symptoms. Cyclic progestin will cause predictable monthly bleeding. Continuous progestogen may cause irregular spotting and bleeding that may persist for many months even in women who have been amenorrheic for some time. Many women will end up switching back to cyclic HT to achieve a more predictable bleeding pattern.
- Raloxifene may aggravate hot flashes in some women.
- Bisphosphonates may cause esophageal irritation.
- Calcitonin nasal spray is expensive and may cause nasal irritation.
- Possible risks and side effects of androgen therapy include increased risk of cardiovascular problems, liver toxicity, development of masculine traits such as increased hair growth and deeper voice changes, and acne.

Risks and Side Effects Associated with Non-Food and Drug Administration (FDA)-Approved HT Treatments

See Annotation Appendix D in the original guideline document for a list of risks and side effects for non-FDA-approved HT treatments.

CONTRAINDICATIONS

CONTRAINDICATIONS

Absolute Contraindications

- Unexplained vaginal bleeding and pregnancy are temporary but absolute contraindications to hormone therapy (HT).
- A past history of breast cancer, endometrial cancer, or venous thrombosis is usually considered absolute contraindication to HT.
- Hypertriglyceridemia is a contraindication to oral conjugated estrogens because of the danger of precipitating pancreatitis. It is safe to use transdermal estrogen, esterified estrogens and estradiol in these patients. (See Discussion #3: "Discuss HT Risks and Contraindications" in the original guideline document for details.)
- Liver disease is a contraindication to androgen therapy.

Relative Contraindications

- Chronic liver disease is a relative contraindication to HT. Transdermal and intra-vaginal estrogen avoids the first pass hepatic effect of oral HT.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These clinical guidelines are designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situations and any specific medical questions.
- With the early termination of one arm of the Women's Health Initiative (WHI) trial in July 2002, and the attendant media coverage, apprehension about hormone therapy has steadily increased. Discrepancies among the various studies continue to be debated, and it is unlikely that definitive information or consensus will be available anytime soon, if ever. The fact remains that neither the known or postulated benefits of long-term hormone therapy (HT) for prevention can be proven to outweigh the potential risks associated with its use. On the other hand, there is no rational basis for the extreme view that HT is of such high or unique risk that it has no role in clinical care, particularly for menopausal symptom relief. Given this uncertainty, careful consideration and more in-depth discussion are required whenever the initiation or continuation of hormone therapy is considered. Women should be fully informed of the strongest available evidence regarding the benefits and risks of HT. The health status of every woman should be thoroughly evaluated so that informed decisions about HT use can be made. Truly collaborative decision-making requires that each woman clarify her individual values and priorities, with help from her provider if she wishes, so that she may decide how important each of the potential benefits and risks of HT is to her unique situation.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for release, a member group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

The following detailed measurement strategies are presented to help close the gap between clinical practice and the guideline recommendations.

Priority Aims for Medical Groups When Using This Guideline

1. Increase the percentage of perimenopausal women who receive education describing risk and benefits of HT.

   Possible measures of accomplishing this aim:

   a. Percentage of perimenopausal/menopausal women whose goals and priorities related to menopausal symptoms have been documented in the medical record
   b. Percentage of perimenopausal/menopausal women who have documentation of general education describing the risks and benefits of hormone therapy (HT) in the medical record
   c. Percentage of women receiving HT who have been re-evaluated of the need for HT documented in the medical record
   d. Percentage of women with osteoporosis or risk factors for osteoporosis who have had a bone mineral density (BMD) after cessation of HT
2. Increase provider understanding of patient decisions regarding the use of HT.

   Possible measures of accomplishing this aim:

   a. List reasons for using HT.
   b. List the risks of using HT.

At this point in development for this guideline, there are no specifications written for possible measures listed above. The Institute for Clinical Systems Improvement (ICSI) will seek input from the medical groups on what measures are of most use as they implement the guideline. In a future revision of the guideline, measurement specifications may be included.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Menopause and hormone therapy (HT): collaborative decision-making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2003 Oct. 62 p. [138 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2003 Oct)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health

Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; e-mail: icsi.info@icsi.org; Web site: www.icsi.org.

SOURCE(S) OF FUNDING

The following Minnesota health plans provide direct financial support: Blue Cross and Blue Shield of Minnesota, HealthPartners, Medica, Metropolitan Health Plan, PreferredOne, and UCare Minnesota. In-kind support is provided by the Institute for Clinical Systems Improvement's (ICSI) members.

GUIDELINE COMMITTEE

Ob/Gyn Steering Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Work Group Members: John M. Wilkinson, MD (Work Group Leader) (Mayo Clinic) (Family Practice); J. Michael Gonzalez-Campoy, MD, PhD (Aspen Medical Group) (Endocrinology); Mary Amon, MD (Family Practice Medical Center) (Family Practice); Dale Akkerman, MD (Park Nicollet Health Services) (Ob/Gyn); Andrew Good, MD (Mayo Clinic) (Ob/Gyn); Richard Kopher, MD (HealthPartners Medical Group) (Ob/Gyn); June LaValleur, MD (University of Minnesota Physicians) (Ob/Gyn); Denise Novak, (Fairview Red Wing Regional Health Center) (Women's Health Nurse Practitioner); Jodi A. Chaffin, RPh (HealthPartners Medical Group) (Herbal Resource Pharmacist); Dianne Eggen, MPH (HealthPartners Health Plan) (Health Education); Sharon MacDonald (Patient Representative); Beth Green, MBA, RRT (Institute for Clinical Systems Improvement) (Implementation and Measurement Advisor); Peter Lynch, MPH (Institute for Clinical Systems Improvement) (Evidence Analyst); Barbara Mullikins, MS (Institute for Clinical Systems Improvement) (Facilitator)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

In the interest of full disclosure, the Institute for Clinical Systems Improvement (ICSI) has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline. Readers of the guideline may assume that only work group members listed below have potential conflict of interest to disclose.

No work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previously released version: Menopause and hormone replacement therapy (HRT): collaborative decision making and management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2002 Oct. 56 p.

The next scheduled revision will occur within 18 months.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Menopause and hormone replacement therapy (HRT): collaborative decision-making and management. In: ICSI pocket guidelines. April 2003 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2003 Mar. pp. 158-166.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

The following are available:

- Appendix B: Hormone Therapy (HT) and Breast Health (handout)
- Appendix C: Androgen Therapy (handout)

Electronic copies are available in the original guideline document available from the Institute for Clinical Systems Improvement (ICSI) Web site. Print copies are available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By

providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on July 10, 2000. The information was verified by the guideline developer on April 25, 2001. This summary was updated on January 15, 2002. The information was verified by the guideline developer on February 1, 2002. This summary was updated again by ECRI on May 4, 2004.

COPYRIGHT STATEMENT

Date Modified: 11/8/2004